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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,656	10/24/2003	Igor Dozmorov	OMRF:013US	9649

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EXAMINER

MILLER, MARINA I

ART UNIT PAPER NUMBER

1631

DATE MAILED: 11/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

10/693,656

Applicant(s)

DOZMOROV ET AL.

Examiner

Marina Miller

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 29 March 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-13 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-13 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 24 October 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>2/27/04; 5/2/05</u> . | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

Applicants' submission filed on 3/29/2004 is acknowledged. Claims 1-13 are pending.

Claims 1-13 presently are under examination.

#### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-13 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

A method of claim 1 is directed to a method for associative analysis comprising collecting expression profiles of control and experimental groups, normalizing expression profiles of control and experimental groups relative to their backgrounds, adjusting expression profiles to identify outliers and to re-scale to an average profile of the control group, identifying similarly expressed groups from the control group, identifying expressed genes by t-tests, and classifying expressed genes as likely false positive, real positive, and potential positive using a t-test. The specification on p. 20 discloses that the instant invention is useful for identifying molecular pathways or classifying disease subphenotypes. However the disclosed utility is not applicable to the instant claims. For example, the result of the claimed methods is the classification of an expression profile based on the association between control and experimental profiles. Classifying real and false positives may have a substantial utility. However, the specification does not disclose any specific utility for the invention because the claims do not recite an array features and what trait, disease, or phenotype is being defined (*i.e.*, what the expressed genes are "positive" for). In order for the result of the method to be used for

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identifying molecular pathways or classifying disease subphenotypes, one skilled in the art must be aware of the correlation between the information received and a condition to be diagnosed. Absent any disclosure for what the classified gene expression represents and/or a correlation between the signal “received” and a disease to be diagnosed, the asserted utility is not specific. No such information is recited in the instant claims. Applicant is reminded that a “use” to perform further research is not a utility under 35 U.S.C. 101. For the reasons set forth above, the invention lacks a specific utility, and therefore lacks a patentable utility.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-113 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation “to identify outliers and to re-scale.” It is not clear whether “identifying” and “re-scaling” are intended to be active, positive method steps. As the intended limitation is not clear, claim 1 is indefinite. Claims 2-13 depend from claim 1, and therefore are indefinite.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1 and 3-13 are rejected under 35 U.S.C. 102(a) as being anticipated by Dozmorov, *Physiol. Genomics*, 12:239-250 (2003), first published 12/19/2002.

Dozmorov discloses a method for statistical analysis of gene expression profiles (239-240). Dozmorov discloses steps of collecting expression profiles of a control and experimental groups (p. 240, *Methods*), normalizing expression profiles of control and experimental groups (p. 241, fig. 1.), adjusting expression profiles to identify outliers and to re-scale to an average profile of the control group (*see Data Normalization and Analysis*, p. 241-242, fig. 1), identifying similarly expressed groups from the control group (p.242, fig. 2.), identifying expressed genes by a t-test (p.242-243, *Identification of Differentially Expressed Genes*), and classifying expressed genes as false positive using a paired and an associative t-test (*e.g.*, likely false positive, real positive, and potential positive, p. 243). Thus, Dozmorov anticipates claims 1, 8, 10, and 13. Dozmorov discloses selecting genes that are expressed above a background and scaling expression profiles to an average profile of the control group (p. 242), thus anticipating claim 3. Dozmorov discloses adjusting profiles by applying regression analysis and a deviation from an average profile (squared deviation) (p. 241-242, fig. 1), thus anticipating claims 4-5. Dozmorov discloses a test based on F-criteria (p. 243, left col.), thus anticipating claim 6. Dozmorov discloses a normal distribution of residuals based on a Kolmogorov-Smirnov criterion (p. 242, left col.). Dozmorov discloses an array (p. 240, left col.), thus anticipating claim 9. Dozmorov discloses testing after identifying genes by the associative t-test (p. 243, left col.), thus anticipating claim 11. Dozmorov discloses excluding outliers (p. 242, left col.), thus anticipating claim 12.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-4, 8-9, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dozmorov, *J. Gerontol.*, 57A(3):B99-B108 (2002), in view of Alters, US 2002/0072484.

Dozmorov discloses a method for evaluating differential gene expression profiles in liver of *dw/dw* mice compared to control mice (p. B99). Dozmorov's method comprises steps of collecting expression profiles of a control and experimental groups (p. B100, left col.), normalizing expression profiles of control and experimental groups (p. B100, right col.), adjusting expression profiles to identify outliers and to re-scale to an average profile of the control group (p. B100, right col.), identifying similarly expressed groups from the control group (p. B100, right col.), identifying expressed genes by a t-test (p. B101), and classifying expressed genes as false positive using a t-test (*e.g.*, false discovery rate, type I and type II error, p. B101, left col. and p. B102, right col.). Dozmorov discloses a Bonferroni t-test (p. B101, B106). Dozmorov discloses selecting genes that are expressed above a background (p. B100) and scaling expression profiles to an average profile of the control group (p. B100, right col.). Dozmorov discloses adjusting profiles by applying regression analysis and a deviation from an average profile (squared deviation) (p. B100, right col. through B101, left col.). Dozmorov discloses an array of expression profiles (p. B100, left col.). Dozmorov discloses exclusion of outliers from expression profiles of the control group (*see*, for example, fig. 2,

Although Dozmorov discloses a two-tail Student's t-test, he does not specifically disclose a paired t-test and a t-test where expression profiles are compared for the entire population (associative t-test).

Alters discloses a method of identifying a candidate drug for treating diseases [0015] wherein different sub-populations are treated with a drug and samples obtained from individuals are assessed for expression of biological markers. Following a data acquisition, variables are analyzed statistically by paired t-test, Bonferroni method, and t-test comparing the entire population (associative t-test).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Dozmorov to use various t-tests, such as taught by Alters, where the motivation would have been to improve a method for detecting effective drugs and to detect statistically significant changes found in an experimental group compare to a control group, as taught by Alters, [0012], [0031].

Claims 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dozmorov, *J. Gerontol.*, 57A(3):B99-B108 (2002), in view of Alters, US 2002/0072484, as applied to claims 1-4, 8-9, and 12 above, and further in view of Wu, *J. Pathol.*, 195:53-65 (2001).

Dozmorov and Alters make obvious a method of claims 1-4 and 8-9, as set forth above.

Dozmorov and Alters do not F-test and a normal distribution of replicates.

Wu discloses analyzing gene expression data from a DNA array to identify candidate genes. Wu discloses F-test and a normal distribution of replicates (fig. 3 and p. 60). Wu discloses a paired t-test (p. 58). Wu discloses normalizing by regression analysis and deviation from a

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regression line calculated against an average profile (*see Bias correction* section, p. 55-56). Wu discloses a threshold value set for expression profiles of housekeeping genes (*i.e.*, excluding outliers from expression profiles of similarly expressed genes, p. 56).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Dozmorov and Alters to use F-test, such as taught by Wu, where the motivation would have been to apply the method to multiple sets of replicate, as taught by Wu, p. 60. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Dozmorov and Alters to use normal distribution of replicates, such as taught by Wu, where the motivation would have been to follow a usual and common assumption of normal distribution for replicates which are usually relatively homogeneous, as taught by Wu, p. 58.

### ***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marina Miller whose telephone number is (571)272-6101. The examiner can normally be reached on 8-5, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph. D., can be reached on (571)272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.



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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**MARJORIE A. MORAN**  
**PRIMARY EXAMINER**

Marina Miller  
Examiner  
Art Unit 1631

MM

*Marjorie A. Moran*  
*9/26/05*